

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P006533WO CTH	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01091	International filing date (day/month/year) 22/03/2000	Priority date (day/month/year) 22/03/1999
International Patent Classification (IPC) or national classification and IPC C12N15/867		
Applicant OXFORD BIOMEDICA (UK) LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 20/07/2000	Date of completion of this report 26.04.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01091

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-87 as originally filed

Claims, No.:

1-49 as originally filed

Drawings, sheets:

1/42-42/42 as originally filed

Sequence listing part of the description, pages:

1-4, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

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International application No. PCT/GB00/01091

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

- ☐ copy of the earlier application whose priority has been claimed.
- ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-34, 36, 38, 41, 47-49
	No:	Claims	35, 37, 39, 40, 42-46
Inventive step (IS)	Yes:	Claims	1-34, 36, 38, 41, 47-49
	No:	Claims	35, 37, 39, 40, 42-46
Industrial applicability (IA)	Yes:	Claims	1-33, 35, 36, 38-49
	No:	Claims	34, 37

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/01091

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

II. Priority

Valid for all claims which are identical to those of the priority document.

V. Reasoned statement on Novelty, Inventive Step and Industrial Applicability

The documents mentioned in the present written International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

- Novelty (Art.33(2) PCT)

D4 discloses the pBABE vector series and its precursors. Test plasmid prZNSV(X) is considered to anticipate claim 37, since the functionality of the intron regulates the balance between the expression of 2 NOIs in the target cell.

D5 discloses a vector system based on adenoviruses which enter a primary target cell and therein cause production of retroviral vector particles which then infect secondary cells. D5 anticipates claims 35, 39, 40 and 46, but also claims 42-44 since the terminology "a vector capable of delivering" is ambiguous. In order to explain this - pUC18 can be stated to be capable of delivering any small nucleotide to a cell during transformation therewith. This does not mean that pUC18 must itself already harbour a specific DNA, but it is certainly capable of harbouring it.

D8 discloses the pCI plasmid which anticipates claim 45.

- Inventive Step (Art.33(3) PCT)

Insofar as the claims are limited to split-intron retroviral vectors which only form a functional intron as a result of LTR rearrangement during reverse transcription, inventive step is acknowledged. Although, the prior art teaches that NOIs can be moved in this manner during reverse transcription (see e.g. D7 or D9), movement of splice sites by this manner has not been disclosed or suggested and differs from the moving of promoters in that it involves a pair of interacting sites rather

than a single promoter sequence. Further, the prior art teaches insertion of genes in reverse into vectors to prevent introns being spliced out during vector production (e.g. D6) and thus a skilled person would not necessarily be motivated to look for alternative solutions to this problem as provided by applicant.

- Industrial Applicability (Art.33(4) PCT)

For the assessment of the present claims 34, 37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 34, 37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

VI. Certain documents

In accordance with Rule 70.10, PCT, applicants attention is drawn to the following document(s):

D1: WO-A-99/15683 (Publication date, 01.04.99; Priority date, 25.09.97; Filing date, 23.09.98)

D2: WO-A-99/15684 (Publication date, 01.04.99; Priority date, 23.09.97 & 25.09.97; Filing date, 23.09.98)

Since D1 appears to be effectively identical to the application, it is likely to present extensive novelty problems under Art.54(3) EPC, should the present file enter a European Regional Phase.

VIII. Certain observations

- Clarity (Art.6 PCT)

A non-functional splice donor/acceptor site is considered meaningless - any sequence which does not have one of these functions could be considered as a non-functional site. This problem applies directly or indirectly to the majority of the claims.

Claim 30 - vector of claim 24 cannot make a retroviral particle ?

Claim 36 - does not add any subject-matter (claims what defined in previous claims). Thus superfluous. Same applies to claim 49.

Claim 41 - "split intron configuration" should be explained

Claim 45 - vectors obtained from specific vectors cannot be claimed. The scope of such a claim is absolutely not clear.

Claim 49 - substantially as described herein is unclear in scope and insofar as it is clear it is already covered by the previous claims.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing:

28 September 2000 (28.09.00)

International application No.:

PCT/GB00/01091

Applicant's or agent's file reference:

P006533WOCTH

International filing date:

22 March 2000 (22.03.00)

Priority date:

22 March 1999 (22.03.99)

Applicant:

UDEN, Mark et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International preliminary Examining Authority on:

20 July 2000 (20.07.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

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INTERNATIONAL SEARCH REPORT

International Publication No
PCT/GB 00/01091

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/867 C12N15/861 C12N5/10 C12N7/01 A61K48/00
C12N9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X, L	WO 99 15683 A (KINGSMAN ALAN ; UDEN MARK (GB); KINGSMAN SUSAN (GB); BEBBINGTON CHR) 1 April 1999 (1999-04-01) L: Priority the whole document	1-49
P, X, L	WO 99 15684 A (BINLEY KATIE MARY ; NAYLOR STUART (GB); LEWIS CLAIRE (GB); BEBBINGT) 1 April 1999 (1999-04-01) L: Priority the whole document	1-49
Y	WO 94 29470 A (MASSACHUSETTS INST TECHNOLOGY) 22 December 1994 (1994-12-22) page 13, line 25 - line 32; figure 1 -/--	1-18, 22-34, 36, 49

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

28 July 2000

Date of mailing of the international search report

11/08/2000

Name and mailing address of the ISA

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Authorized officer

Mandl, B

INTERNATIONAL SEARCH REPORT

Inter. Classification No.

PCT/GB 00/01091

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MORGENSTERN J. P. ET AL.: "ADVANCED MAMMALIAN GENE TRANSFER: HIGH TITRE RETROVIRAL VECTORS WITH MULTIPLE DRUG SELECTION MARKERS AND A COMPLEMENTARY HELPER-FREE PACKAGING CELL LINE" NUCLEIC ACIDS RESEARCH, vol. 18, no. 12, 1990, pages 3587-3596, XP000652091 ISSN: 0305-1048 the whole document	1-18, 22-34, 36,49
X	BILBAO G. ET AL.: "Adenoviral/retroviral vector chimeras: a novel strategy to achieve high-efficiency stable transduction in vivo" FASEB JOURNAL, vol. 11, 11 November 1997 (1997-11-11), pages 624-634, XP000857999 ISSN: 0892-6638 the whole document	39,40, 42,44,46
A		35,41,47
X	ZHENG B. ET AL.: "Increment of hFIX expression with endogenous intron 1 in vitro" CELL RESEARCH, vol. 7, no. 1, June 1997 (1997-06), pages 21-29-29, XP002091319 ISSN: 1001-0602 the whole document	37
X	WO 96 28563 A (BAVARIAN NORDIC ;GSF FORSCHUNGSZENTRUM UMWELT (DE); GUENZBURG WALT) 19 September 1996 (1996-09-19) page 8, last paragraph -page 9, last line	38,43
X	PROMEGA PRODUCT CATALOG 1997, 1997, XP002091320 page 254 -page 255	45
A	YU S.-F. ET AL.: "SELF-INACTIVATING RETROVIRAL VECTORS DESIGNED FOR TRANSFER OF WHOLEGENES INTO MAMMALIAN CELLS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 83, no. 10, 1 May 1986 (1986-05-01), pages 3194-3198, XP000566373 ISSN: 0027-8424 the whole document	48
	-/--	

INTERNATIONAL SEARCH REPORT

Intel or Publication No

PCT/GB 00/01091

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BORG K. M. ET AL.: "Activation of a cryptic splice donor in human immunodeficiency virus type-1." JOURNAL OF BIOMEDICAL SCIENCE, vol. 6, no. 1, January 1999 (1999-01), pages 45-52, XP000929565 ISSN: 1021-7770 the whole document -----	1-49
P, X	ISMAIL S. I. ET AL.: "Split-intron retroviral vectors: Enhanced expression with improved safety." JOURNAL OF VIROLOGY, vol. 74, no. 5, March 2000 (2000-03), pages 2365-2371, XP002143657 ISSN: 0022-538X the whole document -----	1-18, 22-38, 45, 48, 49

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-34,36

A retroviral vector comprising a functional splice donor site and a functional splice acceptor site, a retroviral particle obtainable from said retroviral vector, a cell transfected or transduced with said retroviral vector, the use of said retroviral vector for the manufacture of a pharmaceutical composition, and a retroviral pro-vector corresponding to said retroviral vector.

2. Claims: 35,46,47

A delivery system for a retroviral vector or a hybrid viral vector system for in vivo gene delivery.

3. Claim : 37

Use of a functional intron to restrict expression of one or more NOIs within a desired target cell.

4. Claim : 38

Use of a reverse transcriptase to deliver a first NS from the 3' end of a retroviral pro-vector to the 5' end of a retroviral vector such that a functional intron is created upon transduction.

5. Claim : 43

A lentiviral vector system.

6. Claim : 44

An adenoviral vector system.

7. Claim : 45

Vectors or plasmids based on or obtained from any one or more of the entities presented as in pE1splA, pCI-Neo, pE1RevE, pE1HORSE3.1, pE1PEGASUS4, pCI-Rab, pE1Rab.

8. Claim : 48

A self-inactivating retroviral vector comprising a functional splice donor site and a functional splice

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

acceptor site.

9. Claim : 49

a retroviral vector capable of differential expression of
NOIs in target cells.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte. Application No

PCT/GB 00/01091

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9915683	A	01-04-1999	AU 9175698 A	12-04-1999
			AU 9356298 A	12-04-1999
			EP 1017837 A	12-07-2000
			EP 1017838 A	12-07-2000
			GB 2344592 A	14-06-2000
			GB 2345063 A	28-06-2000
			WO 9915684 A	01-04-1999
			NO 20001486 A	25-05-2000
			NO 20001487 A	23-05-2000
WO 9915684	A	01-04-1999	AU 9356298 A	12-04-1999
			EP 1017838 A	12-07-2000
			GB 2345063 A	28-06-2000
			NO 20001487 A	23-05-2000
			AU 9175698 A	12-04-1999
			EP 1017837 A	12-07-2000
			GB 2344592 A	14-06-2000
			WO 9915683 A	01-04-1999
			NO 20001486 A	25-05-2000
WO 9429470	A	22-12-1994	US 5631162 A	20-05-1997
			CA 2164953 A	22-12-1994
			EP 0706575 A	17-04-1996
			JP 9501046 T	04-02-1997
WO 9628563	A	19-09-1996	AU 5103996 A	02-10-1996
			EP 0817858 A	14-01-1998
			JP 11503305 T	26-03-1999